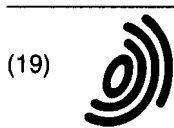


BY



Europäisches Patentamt  
European Patent Office  
Office européen des brevets



(11)

**EP 1 734 039 A1**

(12)

**EUROPEAN PATENT APPLICATION**

(43) Date of publication:  
20.12.2006 Bulletin 2006/51

(21) Application number: 05012616.8

(22) Date of filing: 13.06.2005

(51) Int Cl.:

*C07D 295/12* <sup>(2006.01)</sup> *C07C 275/40* <sup>(2006.01)</sup>  
*C07D 249/12* <sup>(2006.01)</sup> *C07D 285/08* <sup>(2006.01)</sup>  
*C07D 295/22* <sup>(2006.01)</sup> *C07D 251/52* <sup>(2006.01)</sup>  
*C07D 495/04* <sup>(2006.01)</sup> *C07D 471/08* <sup>(2006.01)</sup>  
*A61K 31/17* <sup>(2006.01)</sup> *A61K 31/53* <sup>(2006.01)</sup>  
*A61P 25/28* <sup>(2006.01)</sup>

(84) Designated Contracting States:  
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR  
HU IE IS IT LI LT LU MC NL PL PT RO SE SI SK TR  
Designated Extension States:  
AL BA HR LV MK YU

(71) Applicant: Esbatech AG  
8952 Schlieren (CH)

(72) Inventors:

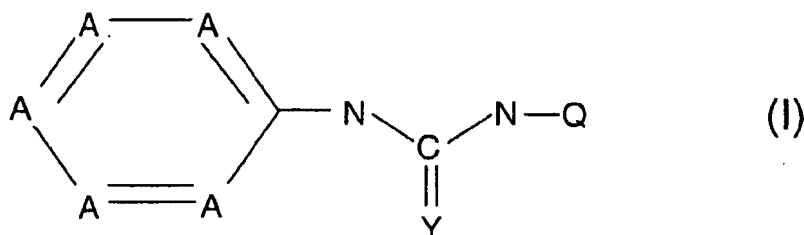
- Lüthi, Urs  
8330 Pfäffikon (CH)
- Danzhi, Huang  
8051 Zürich (CH)
- Kolb, Peter  
8057 Zürich (CH)

- Cecchini, Marco  
8057 Zürich (CH)
- Majeux, Nicolas  
8051 Zürich (CH)
- Dey, Fabian  
8055 Zürich (CH)
- Audétat, Stephan Valentin  
8107 Buchs (CH)
- Caflisch, Amedeo  
8057 Zürich (CH)
- Barberis, Alcide  
8057 Zürich (CH)

(74) Representative: Blum, Rudolf Emil et al  
E. BLUM & CO.  
Vorderberg 11  
8044 Zürich (CH)

(54) Aryl urea compounds as BETA-secretase inhibitors

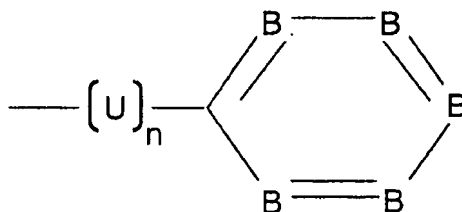
(57) It has been found that compounds of formula I



wherein

A is N or CR, Y is O or S and

Q is an aromatic group or an araliphatic group having the following formula

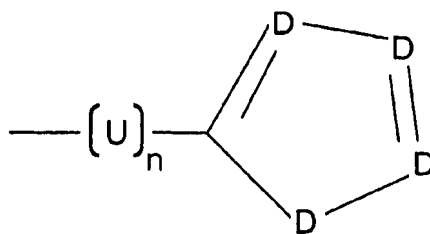


EP 1 734 039 A1

wherein

B = N or CR',

or Q has the following formula



wherein

D = O or S or N or NR<sub>4</sub> or CR<sub>5</sub>

are good  $\beta$ -secretase inhibitors for the treatment of Alzheimer's disease.

**Description**Field of the Invention

- 5 [0001] This invention relates to aryl urea and aryl thiourea compounds, in particular to such compounds acting as beta-secretase inhibitors.

Background Art

- 10 [0002] Alzheimer's disease (AD) is the most common form of dementia among older people, and affects parts of the brain that control thought, memory and language. Susceptibility to Alzheimer's disease increases with age, but Alzheimer's disease is not a normal part of the ageing process.

- [0003] A characteristic of this disease is the presence of extracellular senile plaque, the major component of which is the  $\beta$ -amyloid peptide ( $A\beta$ ). The hydrophobic, 39-43-amino-acid-long  $A\beta$  peptide is excised from the amyloid precursor protein (APP) by sequential cleavage by the so-called  $\beta$ - and  $\gamma$ -secretases.

- 15 [0004] Known genetic predispositions for AD mostly affect genes involved in  $A\beta$  generation or  $A\beta$  deposition. Since the  $A\beta$  peptide seems to play an important role in the pathogenesis of AD, current therapeutic strategies often focus on inhibition of  $A\beta$  deposition and generation. Inhibition of  $\beta$ -secretase activity represents an attractive option to achieve this goal.

- 20 [0005] Despite major efforts to identify novel  $\beta$ -secretase inhibitors by applying in vitro high-throughput screening (HTS) assays with purified soluble BACE-1 fragments and fluorogenic peptide substrates, the best progress towards efficient BACE-1 inhibition has been achieved so far by the use of peptidic transition-state mimetic compounds. However, for efficient inhibition of  $\beta$ -secretase in cells, their molecular weight must be reduced and their structure modified so as to allow for permeation of cellular membranes, the blood-brain barrier and for activity in the natural cellular environment.

- 25 [0006] There also exist some assays for identifying low molecular weight inhibitors of secretases that can block these membrane-bound enzymes at the natural location within intracellular compartments. Cell-based HTS assays, however, are generally faced with the problem that selection signals are often caused by compounds that interfere with cellular processes or pathways that are redundant with that of the target. For example, some compounds found by mammalian cell based assays impair the production of  $A\beta$  through the increase of the pH in intracellular compartments, or they function through protein phosphorylation, or they simply catalyze polymerization of  $A\beta$ , thus reducing the percentage of soluble peptide.

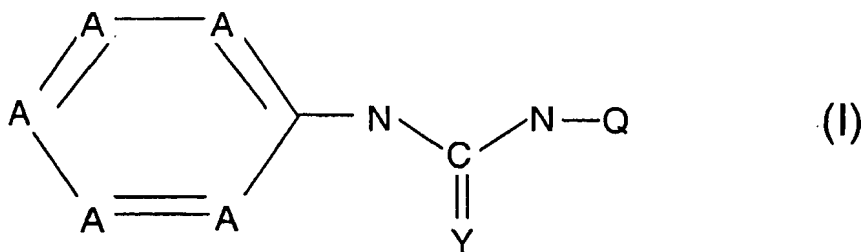
- 30 [0007] Some candidate compounds for inhibiting the production of  $A\beta$  peptide in a biological system have been proposed in US 5,814,646 and US 5,624,937.

- 35 [0008] Nevertheless, there is still a need for potent  $\beta$ -secretase inhibitors that directly inhibit  $\beta$ -secretase.

Disclosure of the Invention

- [0009] Hence, it is a general object of the invention to provide compounds that directly act as  $\beta$ -secretase inhibitors.

- 40 [0010] Now, in order to implement these and still further objects of the invention, which will become more readily apparent as the description proceeds, the  $\beta$ -secretase inhibitors of the present invention are manifested by the following formula I



wherein  
wherein

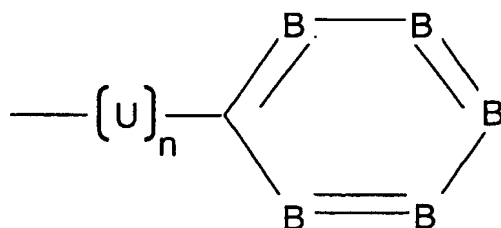
A = N or CR wherein

R is independently from each other selected from H, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, halo-C<sub>1</sub>-C<sub>6</sub>-alkyl, e.g. CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub>-alkyl-carbonyl, halogen, an -NR<sub>2</sub>R<sub>3</sub> group

wherein R<sub>2</sub> and R<sub>3</sub> are independently from each other H, linear or branched C<sub>1</sub>-C<sub>6</sub>-alkyl, in particular linear or branched C<sub>1</sub>-C<sub>4</sub>-alkyl, or R<sub>2</sub> and R<sub>3</sub> form together with the nitrogen to which they are bound an aliphatic or aromatic 5- or 6-membered one or more heteroatoms comprising heterocycle, e.g. a piperidino, a piperazino or a morpholino group, and wherein

Y = O or S,

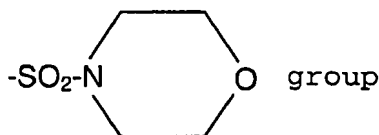
Q = an aromatic group or an araliphatic group having the following formula



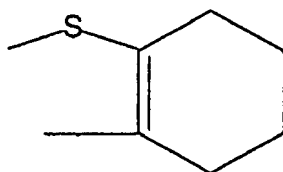
wherein

B = N or CR', wherein

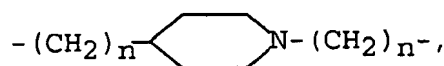
R' is independently from each other selected from the group comprising hydrogen, halogen, in particular F, a C<sub>1</sub>-C<sub>6</sub>-alkyl group, in particular a C<sub>1</sub>-C<sub>4</sub>-alkyl group, an -NR<sub>2</sub>R<sub>3</sub> group wherein R<sub>2</sub> and R<sub>3</sub> are independently from each other H, linear or branched C<sub>1</sub>-C<sub>6</sub>-alkyl, in particular linear or branched C<sub>1</sub>-C<sub>4</sub>-alkyl, or R<sub>2</sub> and R<sub>3</sub> form together with the nitrogen to which they are bound an aliphatic or aromatic 5- or 6-membered one or more heteroatoms comprising heterocycle, e.g. a piperidino, a piperazino or a morpholino group, an amido group, an ester group, a



or two adjacent R' form a group



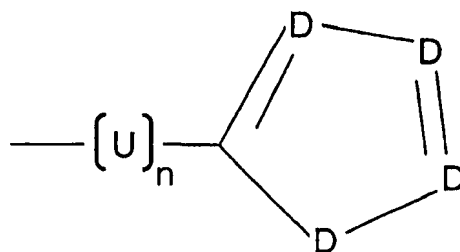
U = -CH<sub>2</sub>-, C=O, -(CH<sub>2</sub>)<sub>n</sub>S-, -(CH<sub>2</sub>)<sub>n</sub>O-, -(CH<sub>2</sub>)<sub>n</sub>NH-, or



wherein the heterocycle is optionally substituted, in particular by one or two C<sub>1</sub>-C<sub>4</sub>-alkyl groups or such that a bicycle is formed, and

n independently from each other is 0, 1 or 2,

or Q has the following formula



wherein

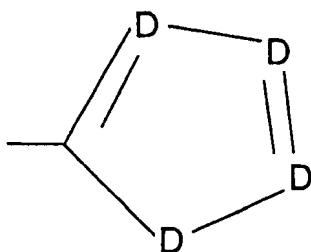
D = O or S or N or NR<sub>4</sub> or CR<sub>5</sub>, wherein

R<sub>4</sub> is linear or branched C<sub>1</sub>-C<sub>6</sub>-alkyl, in particular C<sub>1</sub>-C<sub>4</sub>-alkyl

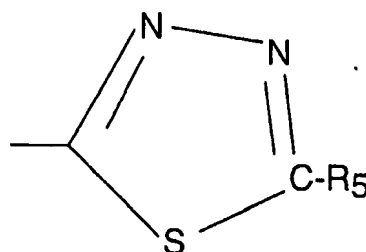
R<sub>5</sub> is independently from each other selected from C<sub>1</sub>-C<sub>6</sub>-alkylthio, aryl-C<sub>1</sub>-C<sub>6</sub>-alkylthio, aryloxy-C<sub>1</sub>-C<sub>6</sub>-alkyl, arylthio-C<sub>1</sub>-C<sub>6</sub>-alkyl, alkyloxy-C<sub>1</sub>-C<sub>6</sub>-alkyl, alkylthio-C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkyloxy, aryl-C<sub>1</sub>-C<sub>6</sub>-alkyloxy and optionally substituted linear or branched C<sub>1</sub>-C<sub>6</sub>-alkyl,

U and n are as defined above,

or pharmaceutically acceptable salts thereof,  
with the proviso that in the case that n is 0 and



is



[0011] R<sub>5</sub> is substituted linear or branched C<sub>1</sub>-C<sub>6</sub>-alkyl, preferably linear or branched C<sub>1</sub>-C<sub>4</sub>-alkyl, with the substituent being selected from O-R<sub>13</sub> or S-R<sub>13</sub> or N-R<sub>13</sub>R<sub>13</sub>' with R<sub>13</sub> and R<sub>13</sub>' being independently selected from the group consisting of unsubstituted or substituted 5- or 6-membered aryl, unsubstituted or substituted 5- or 6-membered heteroaryl, with the substituents of the aryl or heteroaryl group being as defined for R, linear or branched C<sub>1</sub>-C<sub>6</sub>-alkyl and C<sub>5</sub>-C<sub>6</sub>-cycloalkyl, in particular from the group consisting of O-R<sub>13</sub> or S-R<sub>13</sub> with R<sub>13</sub> being selected from the group consisting of 5- or 6-membered aryl, and linear or branched C<sub>1</sub>-C<sub>4</sub>-alkyl.

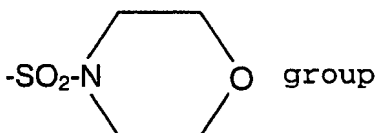
[0012] It has been found that compounds of formula (I) are efficient in inhibiting  $\beta$ -secretase activity. Thus, such compounds are suitable in the treatment and prophylaxis of  $\beta$ -secretase activity related diseases such as Alzheimer's disease, Down's syndrome, and advanced aging of brain.

[0013] In presently slightly preferred inhibitors

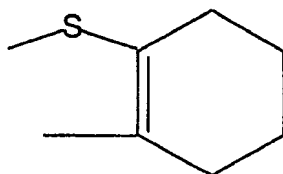
R is independently from each other selected from H, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, halo-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyl, halogen, an -NR<sub>2</sub>R<sub>3</sub> group wherein R<sub>2</sub> and R<sub>3</sub> are independently from each other H or linear or branched C<sub>1</sub>-C<sub>4</sub>-alkyl, or R<sub>2</sub> and R<sub>3</sub> form together with the nitrogen to which they are bound an aliphatic or aromatic 5- or 6-membered one or more heteroatoms comprising heterocycle,

R' is independently from each other selected from the group consisting of hydrogen, halogen, in particular F, a C<sub>1</sub>-C<sub>4</sub>-alkyl group, an -NR<sub>2</sub>R<sub>3</sub> group

wherein R<sub>2</sub> and R<sub>3</sub> are independently from each other H or linear or branched C<sub>1</sub>-C<sub>4</sub>-alkyl, or R<sub>2</sub> and R<sub>3</sub> form together with the nitrogen to which they are bound an aliphatic or aromatic 5- or 6-membered one or more heteroatoms comprising heterocycle, an amido group, an ester group, a



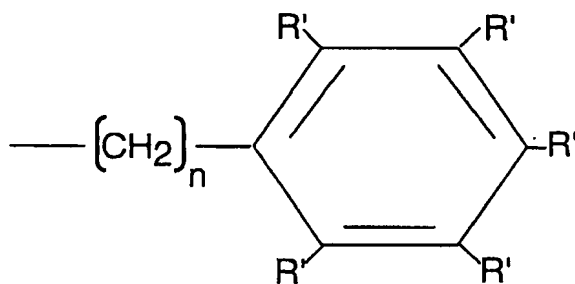
or two adjacent R' form a group



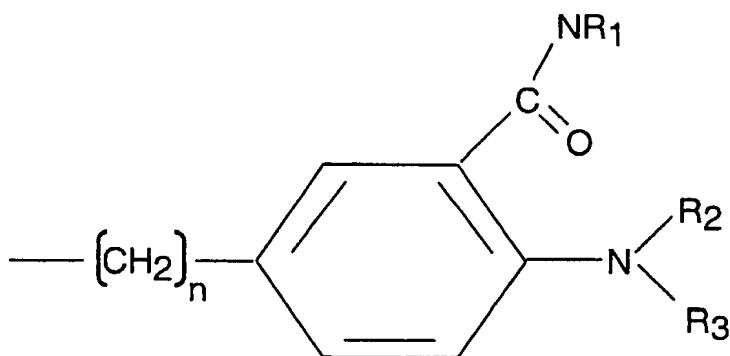
and

R<sub>5</sub> is independently from each other selected from C<sub>1</sub>-C<sub>4</sub>-alkylthio, aryl-C<sub>1</sub>-C<sub>4</sub>-alkylthio, aryloxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, arylthio-C<sub>1</sub>-C<sub>4</sub>-alkyl, alkyloxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, alkylthio-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkyloxy, aryl-C<sub>1</sub>-C<sub>4</sub>-alkyloxy and optionally substituted linear or branched C<sub>1</sub>-C<sub>4</sub>-alkyl, preferably substituted linear or branched C<sub>1</sub>-C<sub>4</sub>-alkyl, with the substituent being selected from O-R<sub>13</sub> or S-R<sub>13</sub> with R<sub>13</sub> being selected from the group consisting of 5- or 6-membered aryl, 5- or 6-membered heteroaryl, linear or branched C<sub>1</sub>-C<sub>4</sub>-alkyl and C<sub>5</sub>-C<sub>6</sub>-cycloalkyl.

[0014] Preferred is a Q that is

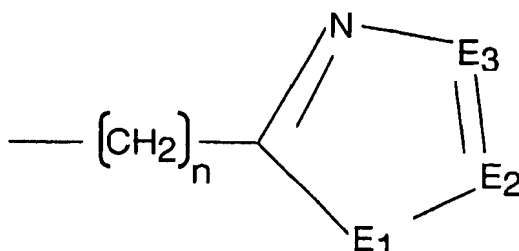


wherein R' and n are as defined above, and especially a Q selected from



wherein

$R_1$  is optionally substituted  $C_1$ - $C_4$ -alkyl,  
 wherein the substituents are selected from optionally halogen substituted aryl,  $C_1$ - $C_4$ -alkoxy, or morpholinyl,  
 $R_2 = C_1$ - $C_6$ -alkyl,  
 $R_3 = C_1$ - $C_6$ -alkyl,  
 or  $R_2$  and  $R_3$  form together with the nitrogen to which they are bound a 5-membered or a 6-membered aliphatic or  
 aromatic ring, and  
 $n = 0, 1$  or  $2$ , whereby in especially preferred embodiments  
 $R_2 = C_1$ - $C_4$ -alkyl, and  
 $R_3 = C_1$ - $C_4$ -alkyl,  
 or Q is



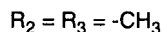
wherein

$E_1 = NR_4$  or S or O, wherein  
 $R_4$  is linear or branched  $C_1$ - $C_4$ -alkyl,  
 $E_2 = CR_5$  or N, wherein  
 $R_5$  is  $C_1$ - $C_4$ -alkylthio, aryl- $C_1$ - $C_4$ -alkylthio, aryloxy- $C_1$ - $C_4$ -alkyl,  
 $E_3 = E_2$  with the proviso that if  $E_2$  is  $CR_5$ ,  $E_3$  is N and if  $E_2$  is N,  $E_3$  is  $CR_5$ , and  
 $n$  is as defined above.

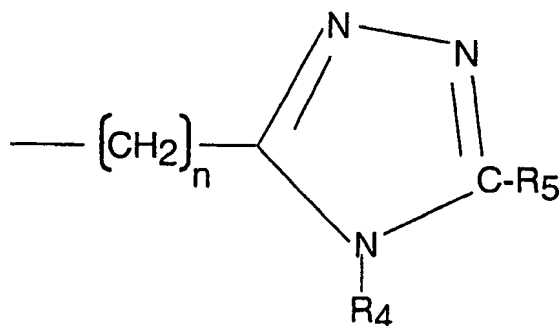
[0015] In a preferred embodiment

$A = CR$ , wherein R is independently selected from H,  $CH_3$ ,  $CH_2CH_3$ ,  $OCH_3$ ,  $COCH_3$ , Cl, Br,  $CF_3$ , more preferred selected from H,  $CH_3$ ,  $CH_2CH_3$ ,  $OCH_3$ , Cl, Br,  $CF_3$ .

[0016] In an also preferred embodiment, Q is 3-amido-4-amino-substituted phenyl as shown above with  
 $R_1 = C_3$ -alkyl,  $C_1$ - $C_4$ -alkoxy- $C_2$ - $C_3$ -alkyl, an optionally p-fluoro substituted phenyl- $C_1$ - $C_4$ -alkyl, and/or



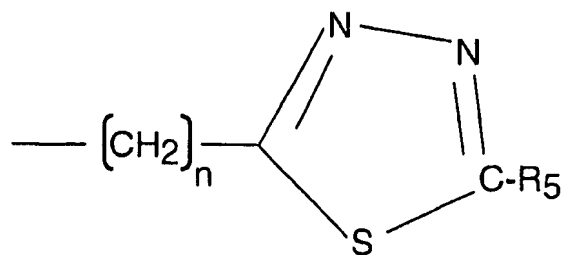
or Q is



wherein

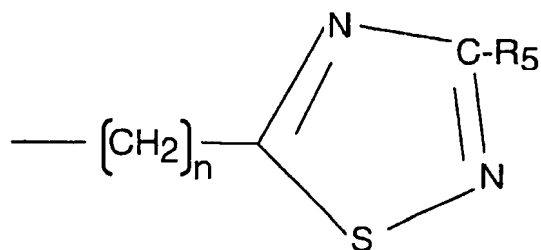
$R_4 =$  linear or branched  $C_1$ - $C_4$ -alkyl, in particular  $CH_3$  or  $-CH(CH_3)_2$

$R_5 = C_1-C_4$ -alkylthio, and  
 $n = 1$  or  $2$ ,  
 or  $Q$  is



wherein

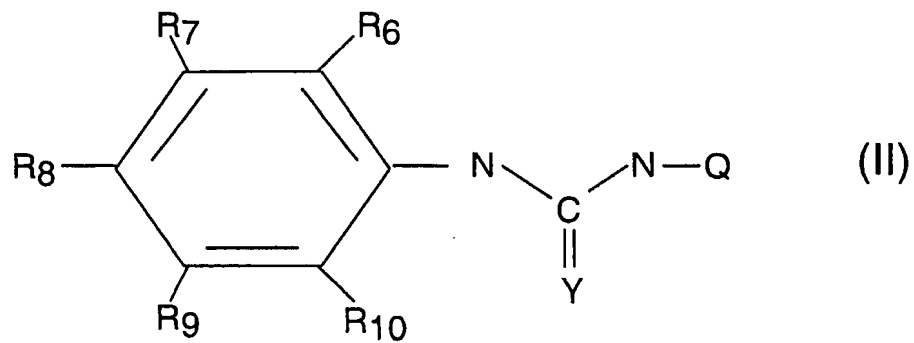
$n = 0$ ,  
 $R_5 =$  aryloxy- $C_1-C_4$  alkyl, in particular phenoxy- $C_1-C_4$  alkyl, especially 1-phenoxy-ethyl,  
 or  $Q$  is



wherein

$n = 0$ ,  
 $R_5 = C_1-C_4$ -alkylthio.

[0017] In a preferred embodiment, the compound is a compound of formula (II)





wherein

$R_6 = \text{H or halogen,}$

$R_7 = \text{H, C}_1\text{-C}_4\text{-alkyl, C}_1\text{-C}_4\text{-alkoxy, C}_1\text{-C}_4\text{-alkylcarbonyl, halo-C}_1\text{-C}_4\text{-alkyl or halogen,}$

$R_8 = \text{H, C}_1\text{-C}_4\text{-alkyl or halogen,}$

$R_9 = \text{H, C}_1\text{-C}_4\text{-alkyl, C}_1\text{-C}_4\text{-alkoxy or halo-C}_1\text{-C}_4\text{-alkyl,}$

$R_{10} = \text{H or halogen, and}$

Y and Q are as defined above.

**[0018]** In more preferred compounds of formula (II)

$R_6 = \text{H or Br,}$

$R_7 = \text{H, C}_1, \text{CH}_3, \text{OCH}_3, \text{CO-CH}_3, \text{CF}_3,$

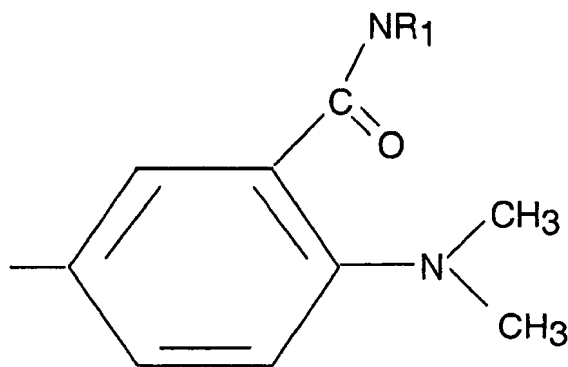
$R_8 = \text{H, CH}_2\text{CH}_3, \text{CH}_3, \text{C}_1,$

$R_9 = \text{H, CH}_3, \text{OCH}_3, \text{CF}_3, \text{ and}$

$R_{10} = \text{H, Br.}$

**[0019]** Also with regard to formula (II) Y and Q are as any Y and Q defined above with regard to formula (I) with the same preferences.

**[0020]** Especially preferred Q are



wherein

$R_1$  is optionally substituted  $\text{C}_1\text{-C}_4\text{-alkyl,}$

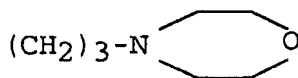
wherein the substituents are selected from optionally halogen substituted aryl,  $\text{C}_1\text{-C}_4\text{-alkoxy, morpholinyl}$

$R_2 = \text{C}_1\text{-C}_4\text{-alkyl}$

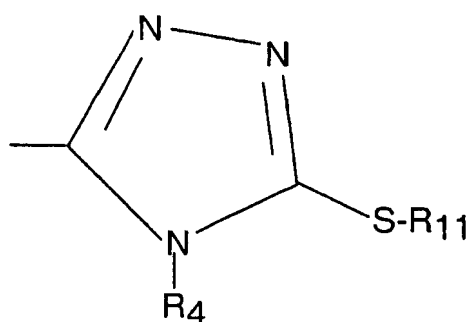
$R_3 = \text{C}_1\text{-C}_4\text{-alkyl, and}$

$n = 0 \text{ or } 1$

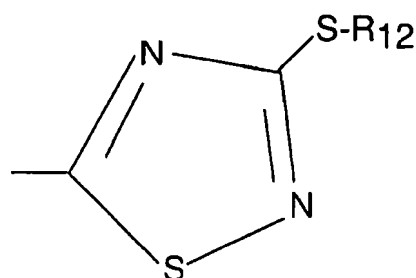
and preferably  $R_1$  is  $\text{CH}_2\text{CH}_2\text{CH}_3, (\text{CH}_2)_3\text{-OCH}_3, (\text{CH}_2)_2\text{-OCH}_3, (\text{CH}_2)_3\text{-OCH}_2\text{CH}_3, \text{CH}_2\text{CH}_2\text{-C}_6\text{H}_5, \text{p-F-benzyl, or}$



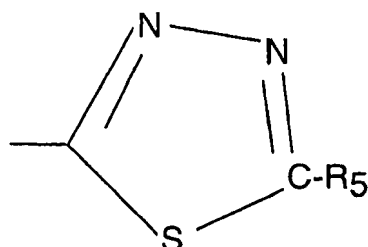
or Q is



15 wherein  $R_4$  is  $\text{CH}_3$ ,  $\text{CH}(\text{CH}_3)_2$ , and  $R_{11}$  is  $\text{CH}_3$ ,  $\text{CH}_2\text{CH}_3$ ,  $\text{CH}_2\text{-C}_6\text{H}_5$ , or Q is



30 wherein  $R_{12}$  is  $\text{CH}_3$  or  $\text{CH}_2\text{CH}_3$ , in particular  $\text{CH}_2\text{CH}_3$  or Q is



45 wherein  $R_5$  is  $-(\text{CH}_2)_m(\text{CR}_{13})(\text{OAr})$ ,

wherein  $R_{13}$  is H,  $\text{C}_1\text{-C}_4\text{-alkyl}$ , in particular methyl, Ar is phenyl or heteroaryl, in particular phenyl, and  $m = 0, 1$  or  $2$ .

[0021] As already mentioned above, the compounds of the present invention can be administered for prophylactic and/or therapeutic treatment of diseases related to the deposition of amyloid beta-protein, such as Alzheimer's disease, Down's syndrome, and advanced aging of the brain. In therapeutic applications, the compounds are administered to a host already suffering from the disease. The compounds will be administered in an amount sufficient to inhibit further deposition of senile plaques. The specific dose of compound(s) administered according to this invention to obtain therapeutic and/or prophylactic effects will, of course, be determined by the particular circumstances, such as the specific compound administered, the condition being treated, etc. A daily dose will contain a dosage level of from about 0.01 mg/kg to about 50 mg/kg of body weight of an active compound, preferably from about 0.05 mg/kg to about 20 mg/kg, for example from about 0.1 mg/kg to about 120 mg/kg.

[0022] The compound can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular and intranasal either as such, but preferable in a formulation comprising carriers adjuvants etc. Suitable pharmaceutically acceptable solid and liquid carriers and/or pharmaceutically acceptable adjuvants, such as stabilizing agents, emulsifiers, etc. are known in the art.

[0023] For example, a typical pharmaceutical composition for intramuscular injection would contain about one  $\mu\text{g}$  to one mg of the compound in from one to four milliliters of sterile buffered water. The typical pharmaceutical composition for intravenous infusion would contain about one to one hundred milligrams of the compound in from one hundred to five hundred milliliters of sterile Ringer's solution.

5 [0024] The pharmaceutical formulations are prepared by known procedures using known and readily available ingredients.

Short Description of the Drawings

10 [0025]

Figure 1 shows the structure formulas of compounds A1 to A14 of Tables 1 and 4

Figure 2 shows the structure formulas of compounds B1 to B4 of Tables 2 and 5

Figure 3 shows the structure formula of compounds C1 to C6 of Tables 3 and 6.

15

Modes for Carrying Out the Invention

[0026] Specific compounds and their  $\beta$ -secretase inhibiting effects are further described below.

[0027] Tables 1 to 3 make a relation between compound designation and structure.

20

25

30

35

40

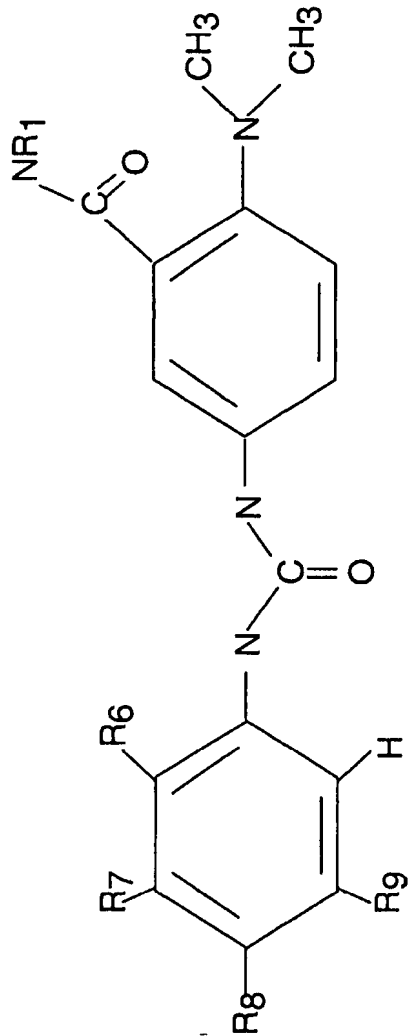
45

50

55

Table 1:

Compound	R <sub>1</sub>	R <sub>6</sub>	R <sub>7</sub>	R <sub>8</sub>	R <sub>9</sub>
A1	(CH <sub>2</sub> ) <sub>3</sub> -N<img alt="morpholine ring" data-bbox="522 595 572 638"/>	H	CF <sub>3</sub>	H	CF <sub>3</sub>
A2	(CH <sub>2</sub> ) <sub>3</sub> -OCH <sub>3</sub>	H	CF <sub>3</sub>	H	CF <sub>3</sub>
A3	(CH <sub>2</sub> ) <sub>3</sub> -OCH <sub>2</sub> CH <sub>3</sub>	H	Cl	H	H
A4	(CH <sub>2</sub> ) <sub>3</sub> -OCH <sub>3</sub>	H	H	H	OCH <sub>3</sub>
A5	(CH <sub>2</sub> ) <sub>2</sub> -CH <sub>3</sub>	H	H	H	OCH <sub>3</sub>
A6	(CH <sub>2</sub> ) <sub>3</sub> -N<img alt="morpholine ring" data-bbox="698 595 748 638"/>	H	H	CH <sub>3</sub>	CH <sub>3</sub>
A7	(CH <sub>2</sub> ) <sub>2</sub> -OCH <sub>3</sub>	H	CH <sub>3</sub>	H	H
A8	(CH <sub>2</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>	H	CH <sub>3</sub>	H	H



5  
10  
15  
20  
25  
30  
35  
40  
45  
50  
55

(continued)

Compound	R <sub>1</sub>	R <sub>6</sub>	R <sub>7</sub>	R <sub>8</sub>	R <sub>9</sub>
A9	(CH <sub>2</sub> ) <sub>3</sub> -OCH <sub>3</sub>		H	Cl	H
A10	CH <sub>2</sub> -p- F- C <sub>6</sub> H <sub>4</sub>		H	OCH <sub>3</sub>	OCH <sub>3</sub>
A11	(CH <sub>2</sub> ) <sub>2</sub> -CH <sub>3</sub>		H	H	H
A12	CH <sub>2</sub> -p- F- C <sub>6</sub> H <sub>4</sub>		H	CF <sub>3</sub>	CF <sub>3</sub>
A13	(CH <sub>2</sub> ) <sub>3</sub> -OCH <sub>3</sub>		H	H	Br
A14	(CH <sub>2</sub> ) <sub>3</sub> OCH <sub>2</sub> CH <sub>3</sub>		Br	H	H

Table 2:

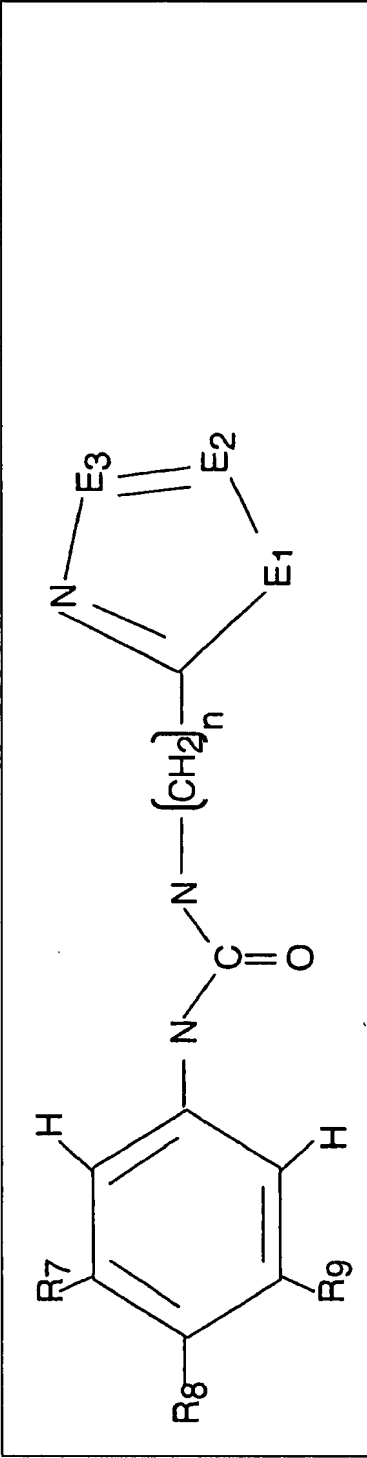
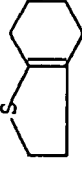



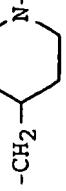
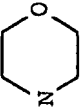

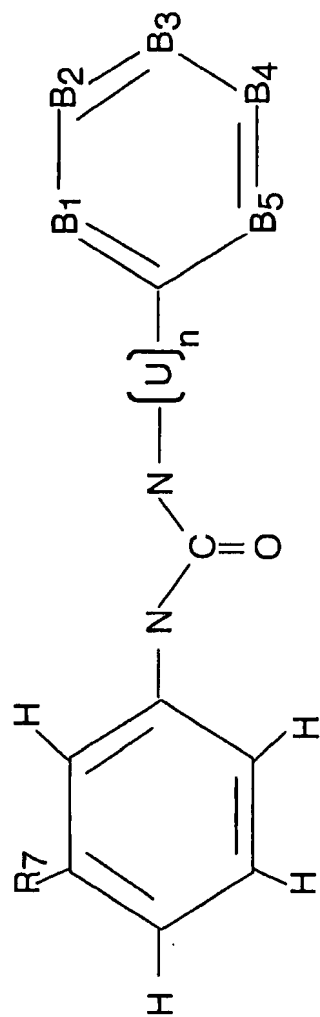
									
Compound	R <sub>7</sub>	R <sub>8</sub>	R <sub>9</sub>	E <sub>1</sub>	R <sub>4</sub>	E <sub>2</sub>	E <sub>3</sub>	R <sub>5</sub>	n
B1	CH <sub>3</sub>	H	CH <sub>3</sub>	NR <sub>4</sub>	CH <sub>3</sub>	CR <sub>5</sub>	N	S-CH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>	1
B2	CF <sub>3</sub>	Cl	H	NR <sub>4</sub>	CH(CH <sub>3</sub> ) <sub>2</sub>	CR <sub>5</sub>	N	S-CH <sub>3</sub>	2
B3	H	H	COCH <sub>3</sub>	S	-	N	CR <sub>5</sub>	S-CH <sub>2</sub> CH <sub>3</sub>	0
B4	OCH <sub>3</sub>	H	H	S	-	CR <sub>5</sub>	N	C(CH <sub>3</sub> )(O-C <sub>6</sub> H <sub>5</sub> )	0

Table 3:

Compo und	R <sub>7</sub>	-[U] <sup>n</sup> -	B <sub>1</sub>	B <sub>2</sub>	B <sub>3</sub>	B <sub>4</sub>	B <sub>5</sub>
C1	OCH <sub>3</sub>	-(CH <sub>2</sub> ) <sub>2</sub> NH-	N	CCH <sub>3</sub>	N		
C2	H	-(CH <sub>2</sub> ) <sub>2</sub> NH-	N	CCH <sub>3</sub>	N		
C3	CH <sub>3</sub>	 -CH <sub>2</sub> -	CH	CH		CH	CH
C4	H	-(CH <sub>2</sub> ) <sub>2</sub> O-	N		N	C-N(CH <sub>3</sub> ) <sub>2</sub>	N
C5	H	-(CH <sub>2</sub> ) <sub>2</sub> O-	N	CNH(CH <sub>2</sub> CH <sub>3</sub> )	N	C-NHC(CH <sub>3</sub> ) <sub>3</sub>	N
C6	COCH <sub>3</sub>	 -CH <sub>2</sub> -	CH	CH	CF	CH	CH



[0028] These compounds have been tested for their performance as  $\beta$ -secretase inhibitors.

[0029] The results of three different tests performed are listed in Tables 4 to 6 below.

[0030] The tests performed were

a) A $\beta$ 1-40 (Sw) bioassay, which measures the amount of the amyloid peptide A $\beta$ 1-40 in the supernatant of Swedish APP695 transgenic HEK293 cells in the presence of the various BACE inhibitors via ELISA (enzyme-linked immunosorbent assay). In the table, the inhibitory concentration that reduces A $\beta$ 1-40 secretion to 50 % is indicated (IC50), or the % reduction of A $\beta$ 1-40 secretion at the indicated concentration.

b) SEAP bioassay, which measures the amount of the secreted reporter enzyme SEAP (secreted alkaline phosphatase) in the supernatant of transiently transfected HEK293 cells. A SEAP-APP(Sw)695 fusion protein is transiently expressed in HEK293 cells in the presence of the various BACE inhibitors. Secretion of the SEAP moiety upon cleavage at the APP  $\beta$ -site is quantitated via a luminescence readout. In the table, the inhibitory concentration that reduces secreted SEAP activity to 50 % is indicated (IC50), or the % reduction of secreted SEAP activity at the indicated concentration.

c) FRET assay, which measures the activity of recombinant BACE enzyme in the presence of the various BACE inhibitors via a FRET (fluorescence resonance energy transfer)-based readout. In the table, the inhibitory concentration that reduces the activity of BACE to 50 % is indicated (IC50), or the % reduction of the activity of BACE at the indicated concentration.

d) An additional in silico test was performed for the compounds listed in Tables 1 to 3. The compounds were docked with the FFLD approach (Budin et al., Biol. Chem. 382, 1365-1372, 2001) and their binding energy was evaluated with the LIECE method (Huang and Caflisch, J. Med. Chem. 47, 5791-5797, 2004). The affinity evaluated with LIECE is in the low micromolar range for most of these compounds.

Table 4

Compound	A $\beta$ 1-40 (Sw) bioassay (cell-based)	SEAP bioassay (cell-based)	FRET assay (in vitro)	LIECE Ki[ $\mu$ M]
A1	IC50 3.0 $\mu$ M	IC50 3.5 $\mu$ M	IC50 58 $\mu$ M	8.11
A2	IC50 3.2 $\mu$ M	27 (3 $\mu$ M)	IC50 284 $\mu$ M	9.35
A3	IC50 2.6 $\mu$ M	23 (3 $\mu$ M)	IC50 97 $\mu$ M	9.81
A4	IC50 7.5 $\mu$ M	21 (6 $\mu$ M)	33 (100 $\mu$ M)	10.26
A5	IC50 14.3 $\mu$ M	0 (6 $\mu$ M)	16 (100 $\mu$ M)	15.99
A6	IC50 23 $\mu$ M	19 (12.5 $\mu$ M)	21 (100 $\mu$ M)	17.56
A7	IC50 12.9 $\mu$ M	0 (12.5 $\mu$ M)	0 (100 $\mu$ M)	18.64
A8	IC50 5.6 $\mu$ M	14 (3 $\mu$ M)	35 (100 $\mu$ M)	32.34
A9	IC50 5.9 $\mu$ M	17 (3 $\mu$ M)	IC50 46 $\mu$ M	32.56
A10	IC50 3.1 $\mu$ M	10 (1.6 $\mu$ M)	IC50 64 $\mu$ M	34.71
A11	IC50 5.2 $\mu$ M	0 (6 $\mu$ M)	20 (200 $\mu$ M)	38.37
A12	IC50 4.2 $\mu$ M	14 (1.6 $\mu$ M)	IC50 131 $\mu$ M	39.41
A13	IC50 3.8 $\mu$ M	25 (3 $\mu$ M)	37 (100 $\mu$ M)	50.09
A14	IC50 7.8 $\mu$ M	0 (6 $\mu$ M)	0 (100 $\mu$ M)	66.41

Table 5:

Compound	A $\beta$ 1-40 (Sw) bioassay (cell-based)	SEAP bioassay (cell-based)	FRET assay (in vitro)	LIECE Ki[ $\mu$ M]
B1	IC50 18 $\mu$ M	0 (50 $\mu$ M)	0 (500 $\mu$ M)	11.85
B2	IC50 40 $\mu$ M	0 (12.5 $\mu$ M)	0 (250 $\mu$ M)	28.53
B3	IC50 1.6 $\mu$ M	IC50 10 $\mu$ M	0 (25 $\mu$ M)	29.60
B4	IC50 13 $\mu$ M	0 (12.5 $\mu$ M)	0 (500 $\mu$ M)	34.97



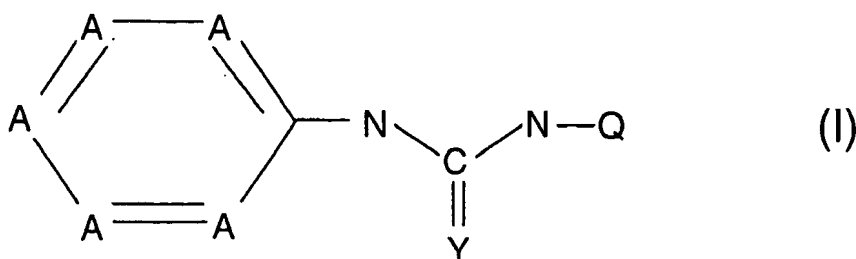
Table 6:

Compo und	A $\beta$ 1-40 (Sw) bioassay (cell-based)	SEAP bioassay (cell-based)	FRET assay (in vitro)	LIECE Ki[ $\mu$ M]
C1	21 (6 $\mu$ M)	0 (12.5 $\mu$ M)	0 (500 $\mu$ M)	15.37
C2	IC50 13 $\mu$ M	0 (12.5 $\mu$ M)	0 (500 $\mu$ M)	33.69
C3	IC50 22 $\mu$ M	0 (12.5 $\mu$ M)	0 (50 $\mu$ M)	15.96
C4	31 (12.5 $\mu$ M)	0 (12.5 $\mu$ M)	0 (500 $\mu$ M)	23.49
C5	IC50 10-20 $\mu$ M	0 (25 $\mu$ M)	0 (500 $\mu$ M)	32.95
C6	22 (25 $\mu$ M)	IC50 35 $\mu$ M	IC50 490 $\mu$ M	48.10

[0031] While there are shown and described presently preferred embodiments of the invention, it is to be distinctly understood that the invention is not limited thereto but may be otherwise variously embodied and practiced within the scope of the following claims.

## Claims

1.  $\beta$ -secretase inhibitors of formula I



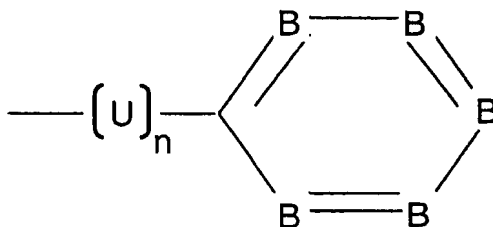
wherein

A = N or CR wherein

R is independently from each other selected from H, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, halo-C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkyl-carbonyl, halogen, an -NR<sub>2</sub>R<sub>3</sub> group wherein R<sub>2</sub> and R<sub>3</sub> are independently from each other H, linear or branched C<sub>1</sub>-C<sub>6</sub>-alkyl, in particular linear or branched C<sub>1</sub>-C<sub>4</sub>-alkyl, or R<sub>2</sub> and R<sub>3</sub> form together with the nitrogen to which they are bound an aliphatic or aromatic 5- or 6-membered one or more heteroatoms comprising heterocycle, and wherein

Y = O or S

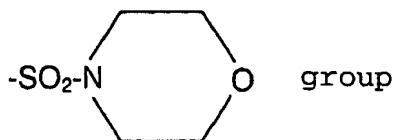
Q = an aromatic group or an araliphatic group having the following formula



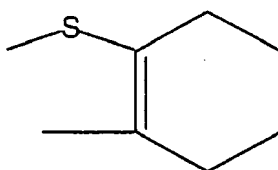
wherein

B = N or CR', wherein

R' is independently from each other selected from the group comprising hydrogen, halogen, in particular F, a C<sub>1</sub>-C<sub>6</sub>-alkyl group, in particular a C<sub>1</sub>-C<sub>4</sub>-alkyl group, an -NR<sub>2</sub>R<sub>3</sub> group wherein R<sub>2</sub> and R<sub>3</sub> are independently from each other H, linear or branched C<sub>1</sub>-C<sub>6</sub>-alkyl, in particular linear or branched C<sub>1</sub>-C<sub>4</sub>-alkyl, or R<sub>2</sub> and R<sub>3</sub> form together with the nitrogen to which they are bound an aliphatic or aromatic 5- or 6-membered one or more heteroatoms comprising heterocycle, an amido group, an ester group, a



or two adjacent R' form the group



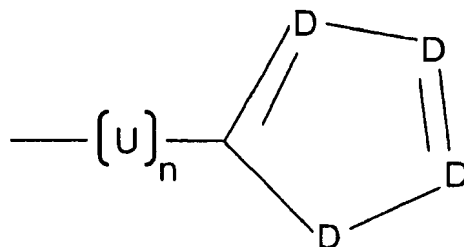
-U- = -CH<sub>2</sub>-, C=O, -(CH<sub>2</sub>)<sub>n</sub>S-, -(CH<sub>2</sub>)<sub>n</sub>O-, -(CH<sub>2</sub>)<sub>n</sub>NH-, or



wherein the heterocycle is optionally substituted, in particular by one or two C<sub>1</sub>-C<sub>4</sub>-alkyl groups, or such that a bicycle is formed, and

n independently from each other is 0, 1 or 2

or Q has the following formula



wherein

D = O or S or N or NR<sub>4</sub> or CR<sub>5</sub>, wherein

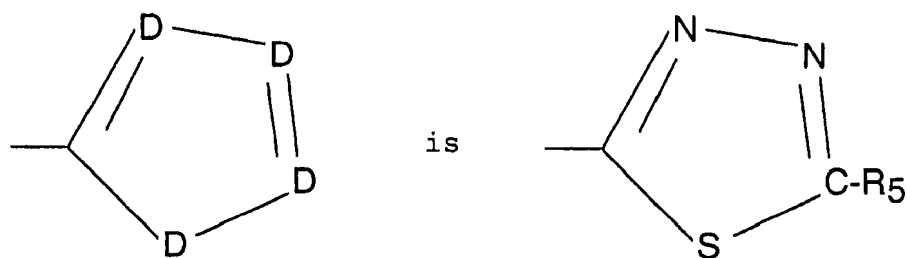
R<sub>4</sub> is linear or branched C<sub>1</sub>-C<sub>6</sub>-alkyl, in particular C<sub>1</sub>-C<sub>4</sub>-alkyl

R<sub>5</sub> is independently from each other selected from C<sub>1</sub>-C<sub>6</sub>-alkylthio, aryl-C<sub>1</sub>-C<sub>6</sub>-alkylthio, aryloxy-C<sub>1</sub>-C<sub>6</sub>-alkyl, arylthio-C<sub>1</sub>-C<sub>6</sub>-alkyl, alkyloxy-C<sub>1</sub>-C<sub>6</sub>-alkyl, alkylthio-C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkyloxy, aryl-C<sub>1</sub>-C<sub>6</sub>-alkyloxy and optionally substituted linear or branched C<sub>1</sub>-C<sub>6</sub>-alkyl,

U and n are as defined above,

or pharmaceutically acceptable salts thereof

as pharmaceutical, with the proviso that in the case that n is 0 and

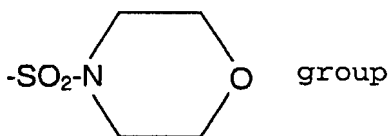


15  $R_5$  is substituted linear or branched  $C_1$ - $C_6$ -alkyl, preferably linear or branched  $C_1$ - $C_4$ -alkyl, with the substituent being selected from  $O-R_{13}$  or  $S-R_{13}$  or  $N-R_{13}R_{13}'$  with  $R_{13}$  and  $R_{13}'$  being independently selected from the group consisting of unsubstituted or substituted 5- or 6-membered aryl, unsubstituted or substituted 5- or 6-membered heteroaryl, with the substituents of the aryl or heteroaryl group being as defined for R, linear or branched  $C_1$ - $C_6$ -alkyl and  $C_5$ - $C_6$ -cycloalkyl, in particular from the group consisting of  $O-R_{13}$  or  $S-R_{13}$  with  $R_{13}$  being selected from the group consisting of 5- or 6-membered aryl, and linear or branched  $C_1$ - $C_4$ -alkyl.

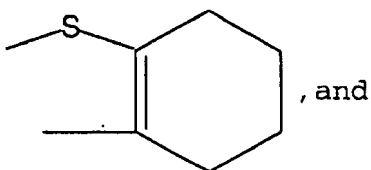
20 2. The  $\beta$ -secretase inhibitors of claim 1, wherein

25 R is independently from each other selected from H,  $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_4$ -alkoxy, halo- $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_4$ -alkyl-carbonyl, halogen, an  $-NR_2R_3$  group wherein  $R_2$  and  $R_3$  are independently from each other H or linear or branched  $C_1$ - $C_4$ -alkyl, or  $R_2$  and  $R_3$  form together with the nitrogen to which they are bound an aliphatic or aromatic 5- or 6-membered one or more heteroatoms comprising heterocycle,

30  $R'$  is independently from each other selected from the group consisting of hydrogen, halogen, in particular F, a  $C_1$ - $C_4$ -alkyl group, an  $-NR_2R_3$  group wherein  $R_2$  and  $R_3$  are independently from each other H or linear or branched  $C_1$ - $C_4$ -alkyl, or  $R_2$  and  $R_3$  form together with the nitrogen to which they are bound an aliphatic or aromatic 5- or 6-membered one or more heteroatoms comprising heterocycle, an amido group, and an ester group, a



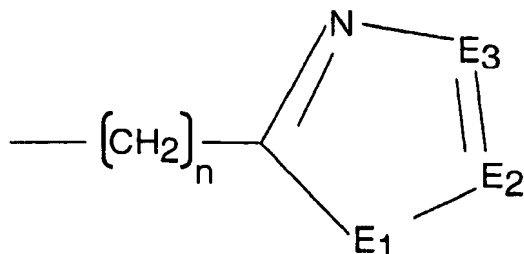
40 or two adjacent  $R'$  form a group



50  $R_5$  is independently from each other selected from  $C_1$ - $C_4$ -alkylthio, aryl- $C_1$ - $C_4$ -alkylthio, aryloxy- $C_1$ - $C_4$ -alkyl, arylthio- $C_1$ - $C_4$ -alkyl, alkyloxy- $C_1$ - $C_4$ -alkyl, alkylthio- $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_4$ -alkyloxy, aryl- $C_1$ - $C_4$ -alkyloxy and optionally substituted linear or branched  $C_1$ - $C_4$ -alkyl, preferably substituted linear or branched  $C_1$ - $C_4$ -alkyl, with the substituent being selected from  $OR_{13}$  or  $S-R_{13}$  with  $R_{13}$  being selected from the group consisting of 5- or 6-membered aryl, 5- or 6-membered heteroaryl, linear or branched  $C_1$ - $C_4$ -alkyl and  $C_5$ - $C_6$ -cycloalkyl.

55 3. The  $\beta$ -secretase inhibitors of claim 1 or 2 wherein Q is an aromatic or araliphatic group as defined above or

Q is



wherein

$E_1 = NR_4$  or S or O, wherein

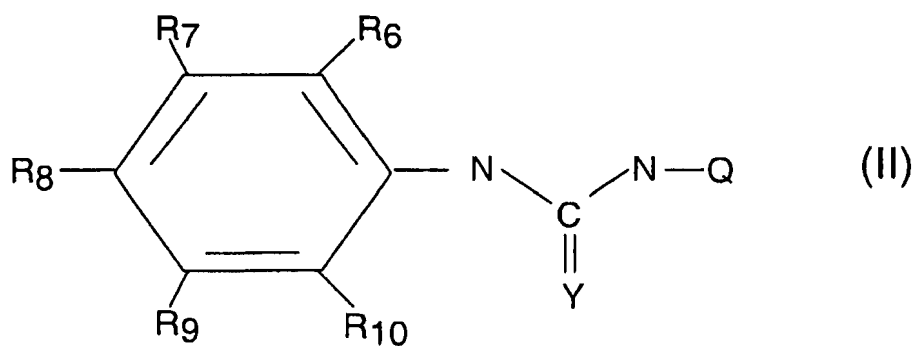
$R_4$  is linear or branched  $C_1$ - $C_4$ -alkyl,

$E_2 = CR_5$  or N, wherein

$R_5$  is  $C_1$ - $C_4$ -alkylthio, aryl- $C_1$ - $C_4$ -alkylthio, aryloxy- $C_1$ - $C_4$ -alkyl,

$E_3 = E_2$  with the proviso that if  $E_2$  is  $CR_5$ ,  $E_3$  is N and if  $E_2$  is N,  $E_3$  is  $CR_5$ , and  $n$  is as defined above.

4. The  $\beta$ -secretase inhibitors of anyone of the preceding claims with formula II



wherein

$R_6 = H$  or halogen

$R_7 = H$ ,  $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_4$ -alkoxy,  $C_1$ - $C_4$ -alkylcarbonyl, halo- $C_1$ - $C_4$ -alkyl or halogen,

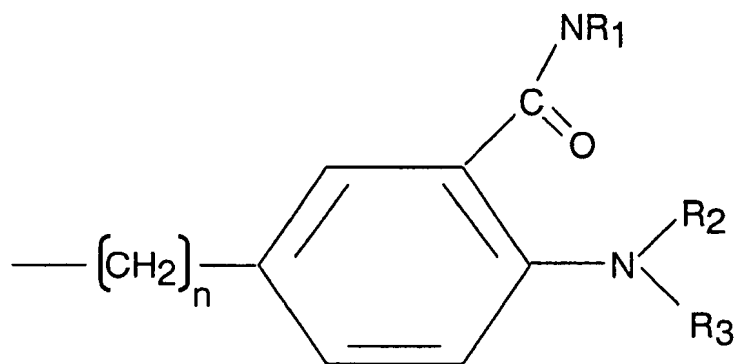
$R_8 = H$ ,  $C_1$ - $C_4$ -alkyl or halogen,

$R_9 = H$ ,  $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_4$ -alkoxy or halo- $C_1$ - $C_4$ -alkyl,

$R_{10} = H$  or halogen

Y and Q are as defined above, and

wherein Q is a group of the following formula



wherein

$R_1$  is optionally substituted  $C_1$ - $C_4$ -alkyl,

wherein the substituents are selected from optionally halogen substituted aryl,  $C_1$ - $C_4$ -alkoxy, morpholinyl,

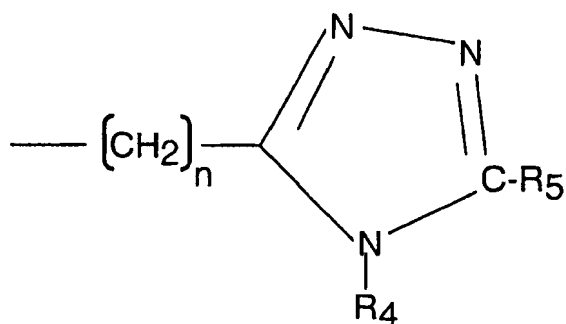
$R_2 = C_1$ - $C_6$ -alkyl,

$R_3 = C_1$ - $C_6$ -alkyl, or

$R_2$  and  $R_3$  form together with the nitrogen to which they are bound a 5-membered or a 6-membered aromatic or aliphatic heterocycle, and

$n = 0, 1$  or  $2$ ,

or Q is a group of the following formula



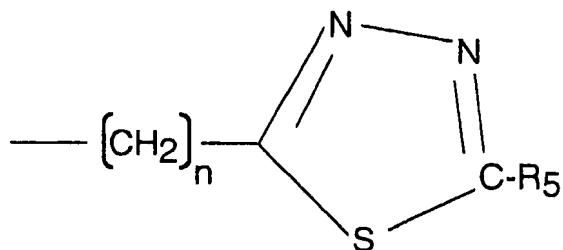
wherein

$R_4 =$  linear or branched  $C_1$ - $C_4$ -alkyl, in particular  $CH_3$  or  $CH(CH_3)_2$ ,

$R_5 =$  is  $C_1$ - $C_4$ -alkylthio or aryl- $C_1$ - $C_4$ -alkylthio, and

$n = 1$  or  $2$ ,

or Q is a group of the following formula

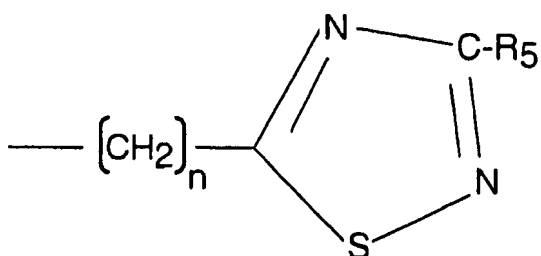


wherein

$n = 0$ ,

$R_5$  = aryloxy- $C_1$ - $C_4$  alkyl, in particular phenoxy- $C_1$ - $C_4$  alkyl, especially 1-phenoxy-ethyl,

or Q is a group of the following formula



wherein

$n = 0$ ,

$R_5$  =  $C_1$ - $C_4$  alkylthio,

or pharmaceutically acceptable salts thereof.

5. The  $\beta$ -secretase inhibitor of claim 4  
wherein

$R_6$  = H or Br,

$R_7$  = H, Cl,  $CH_3$ ,  $OCH_3$ ,  $CO-CH_3$ ,  $CF_3$ ,

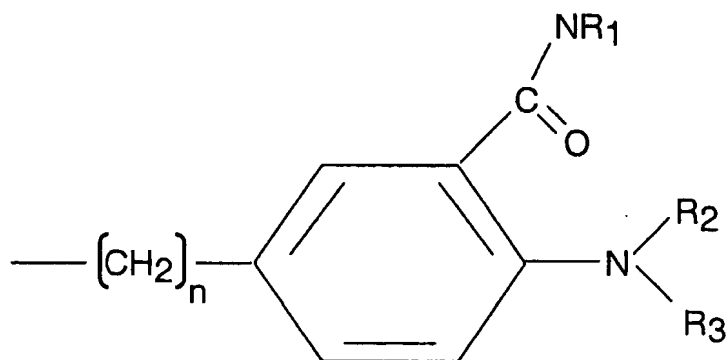
$R_8$  = H,  $CH_2CH_3$ ,  $CH_3$ , Cl,

$R_9$  = H,  $CH_3$ ,  $OCH_3$ ,  $CF_3$ ,

$R_{10}$  = H, Br,

or pharmaceutically acceptable salts thereof.

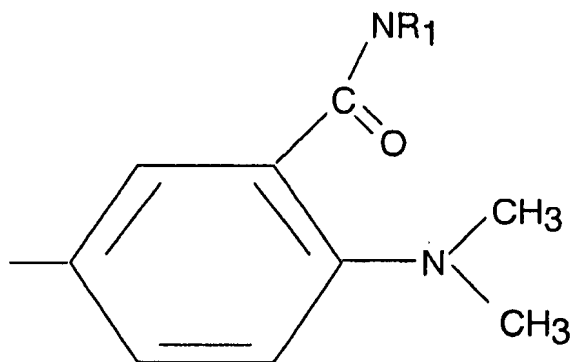
6. The  $\beta$ -secretase inhibitor of claim 4 or 5  
wherein Q is a group of the following formula



wherein

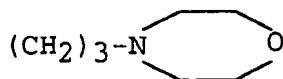
20  $R_1$  is optionally substituted  $C_1$ - $C_4$ -alkyl,  
 wherein the substituents are selected from optionally halogen substituted aryl,  $C_1$ - $C_4$ -alkoxy, morpholinyl,  
 $R_2 = C_1$ - $C_4$ -alkyl,  
 $R_3 = C_1$ - $C_4$ -alkyl, and  
 $n = 0$  or  $1$ .

- 25 7. The  $\beta$ -secretase inhibitor of claim 6,  
 wherein Q is

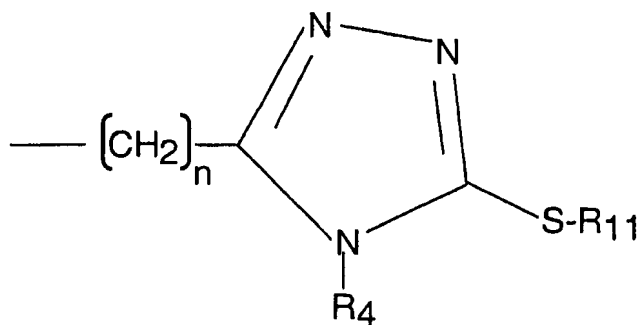


or pharmaceutically acceptable salts thereof.

- 45 8. The  $\beta$ -secretase inhibitor of claim 7,  
 wherein  $R_1$  is  $CH_2CH_2CH_3$ ,  $(CH_2)_3-OCH_3$ ,  $(CH_2)_2-OCH_3$ ,  $(CH_2)_3-OCH_2CH_3$ ,  $CH_2CH_2-C_6H_5$ ,  $CH_2$ -p-F- $C_6H_4$ , or



- 55 9. The  $\beta$ -secretase inhibitor of claim 4 or 5,  
 wherein Q is



15 and wherein

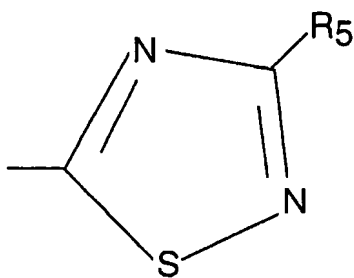
$n$  is 1 or 2,

$\text{R}_4$  is  $\text{CH}_3$ ,  $\text{CH}(\text{CH}_3)_2$ , and

$\text{R}_{11}$  is  $\text{CH}_3$ ,  $\text{CH}_2\text{CH}_3$ ,  $\text{CH}_2\text{-C}_6\text{H}_5$ ,

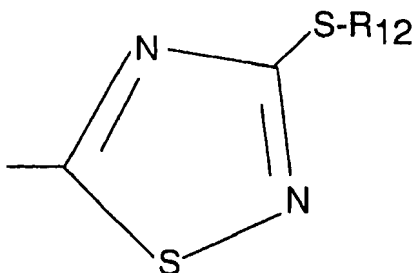
20 or pharmaceutically acceptable salts thereof.

10. The  $\beta$ -secretase inhibitor of claim 4 or 5, wherein Q is



and wherein  $\text{R}_5$  is as defined above,  
or pharmaceutically acceptable salts thereof.

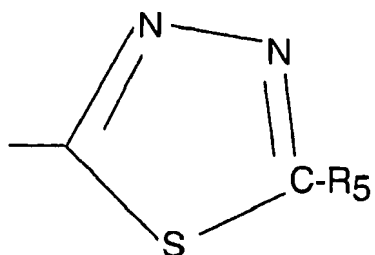
40 11. The  $\beta$ -secretase inhibitor of claim 10,  
wherein Q is



wherein  $\text{R}_{12}$  is  $\text{CH}_3$  or  $\text{CH}_2\text{CH}_3$ , in particular  $\text{CH}_2\text{CH}_3$ ,  
or pharmaceutically acceptable salts thereof.



12. The  $\beta$ -secretase inhibitor of claim 4 or 5, wherein Q is



and wherein  $R_5$  is as defined above,  
or pharmaceutically acceptable salts thereof.

13. The  $\beta$ -secretase inhibitor of claim 12

wherein  $R_5$  is  $(CH_2)_m-(CR_{13})(OAr)$

wherein  $R_{13}$  is H,  $C_1$ - $C_4$ -alkyl, in particular methyl, Ar is phenyl or heteroaryl, in particular phenyl, and  $m = 0, 1$  or  $2$ , or pharmaceutically acceptable salts thereof.

14. Use of a  $\beta$ -secretase inhibitor of anyone of the preceding claims, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting the production and/or the accumulation of amyloid beta-protein in warm blooded mammals, in particular human beings, especially for the treatment of Alzheimer's disease and or Down's syndrome and/or aging of brain.

15. A pharmaceutical composition comprising at least one  $\beta$ -secretase inhibitor of anyone of claims 1 to 13, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier and optionally one or more adjuvants.

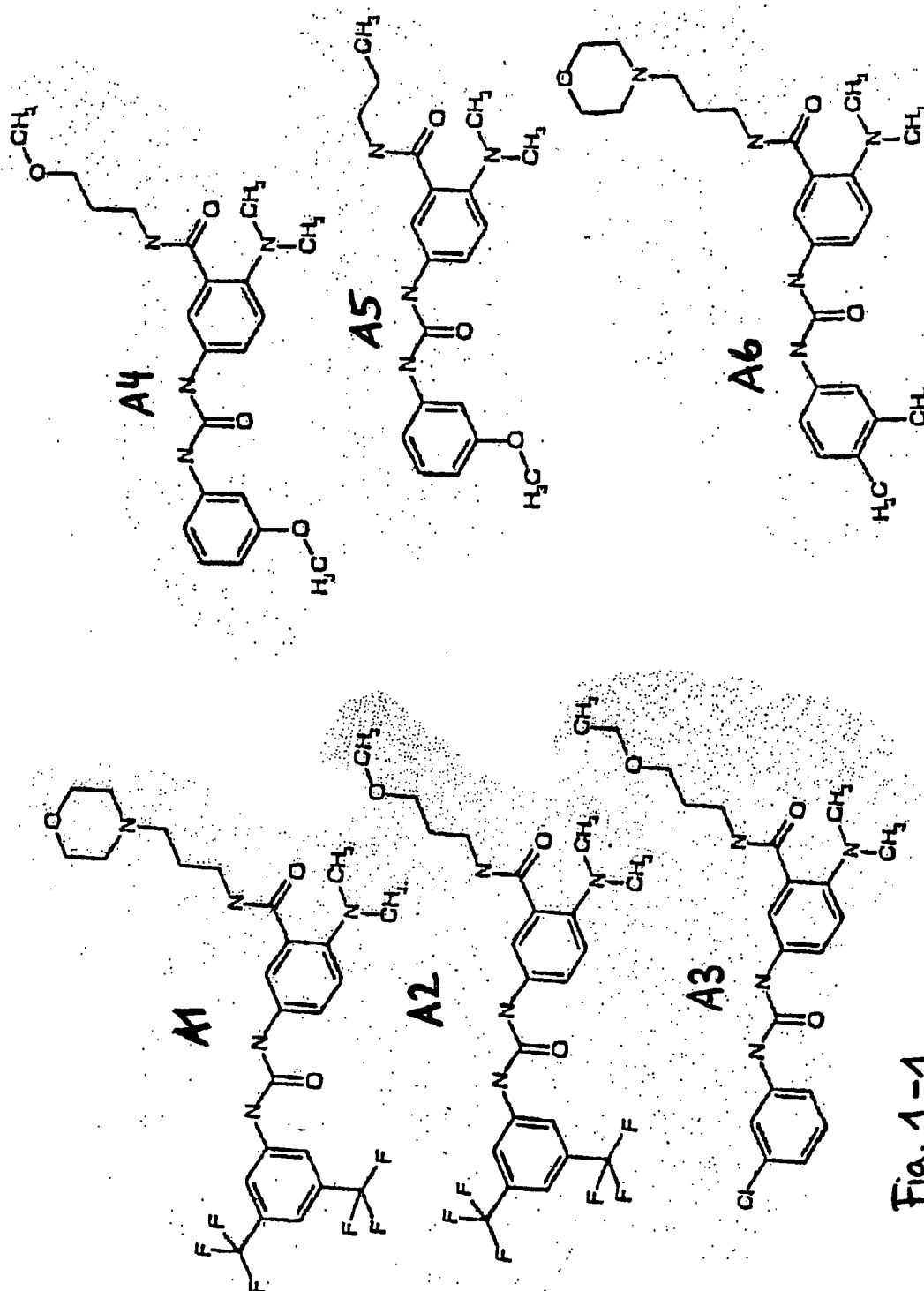


Fig. 1-1

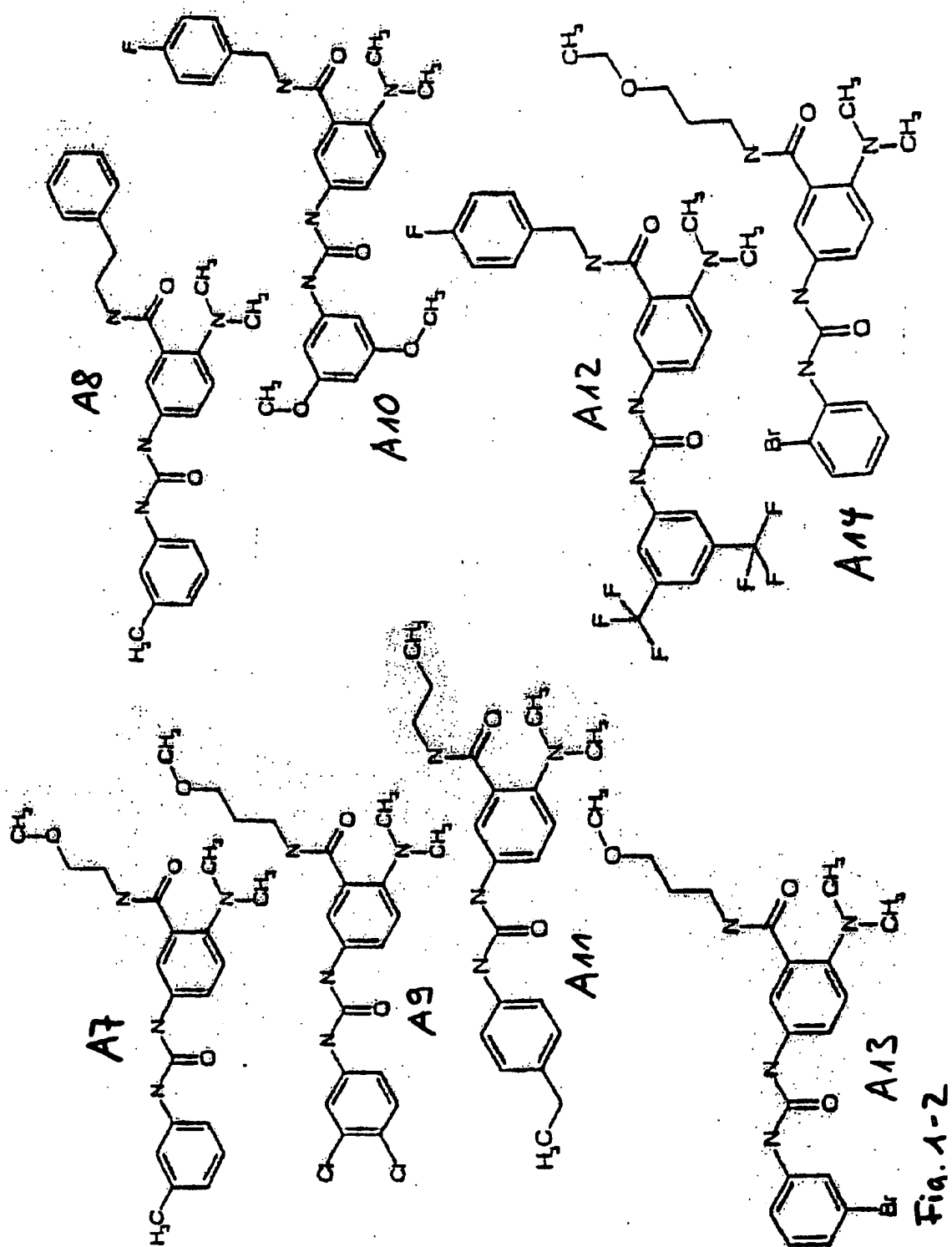


Fig. 1-2

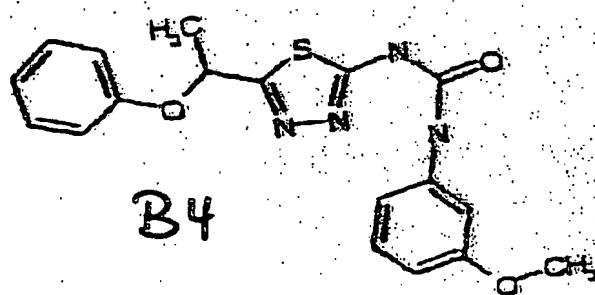
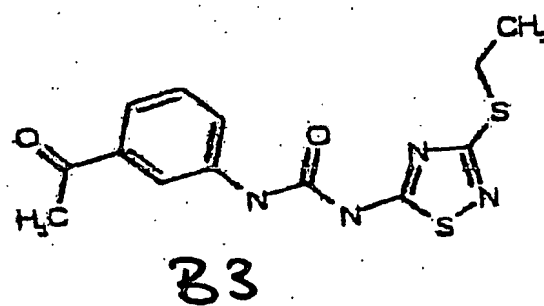
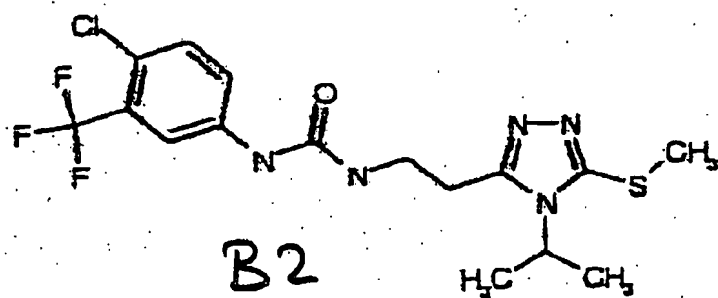
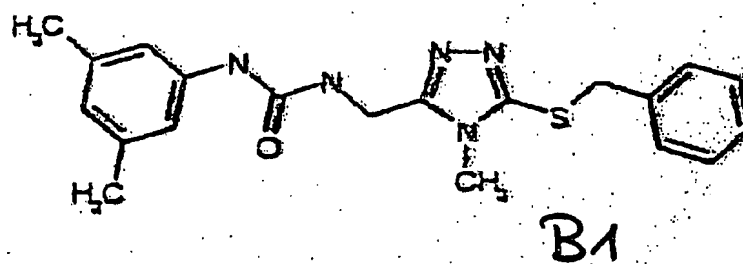


Fig. 2

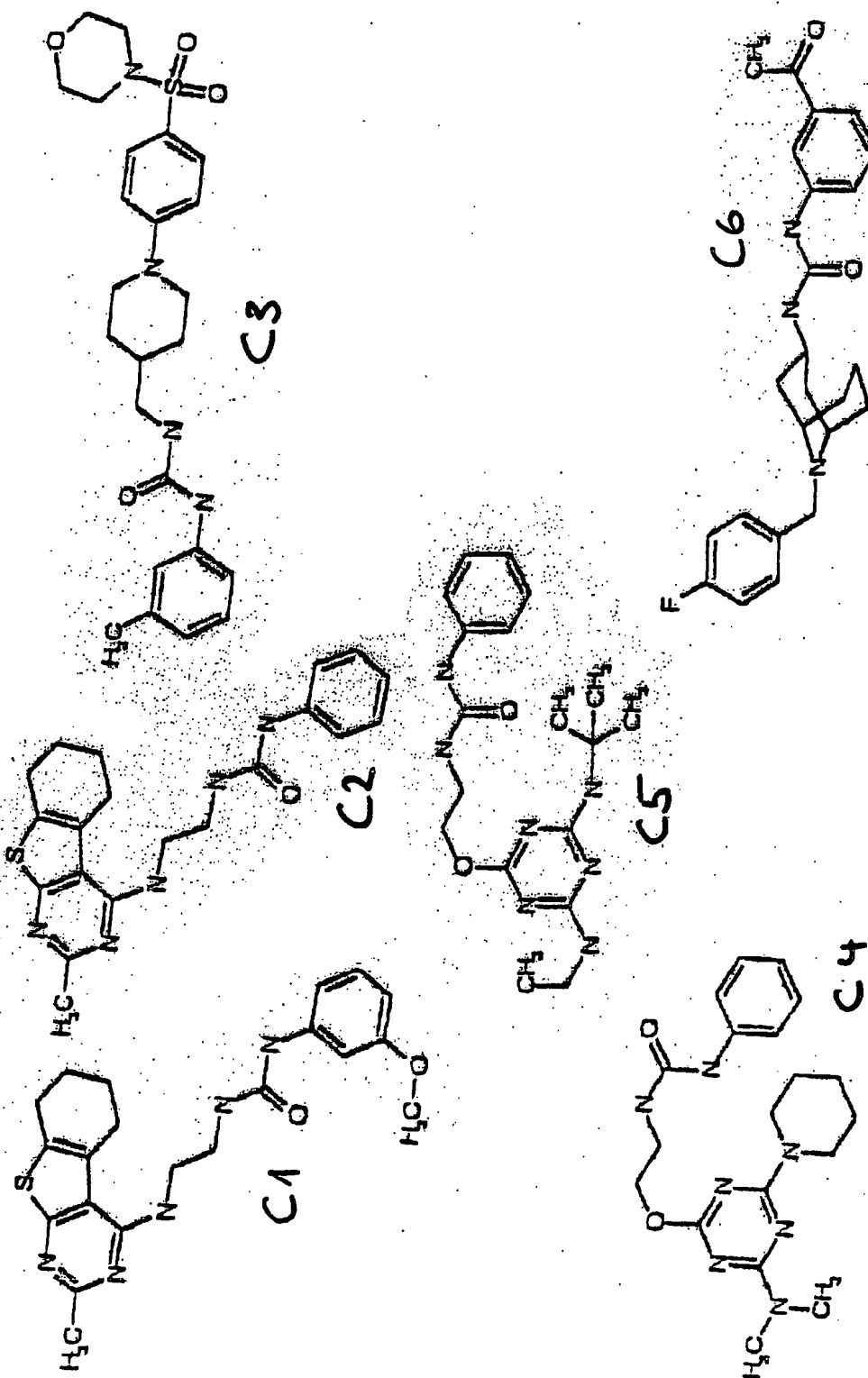


Fig. 3



European Patent  
Office

# PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention EP 05 01 2616 shall be considered, for the purposes of subsequent proceedings, as the European search report

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
D,X	US 5 814 646 A (HEINZ ET AL) 29 September 1998 (1998-09-29) * column 1, line 20 - line 48 * -----	1-15	C07D295/12 C07C275/40 C07D249/12 C07D285/08 C07D295/22 C07D251/52 C07D495/04 C07D471/08 A61K31/17 A61K31/53 A61P25/28
X	DATABASE CHEMCATS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002350888 * order numbers: ASN 10345176, ASN 10344816, ASN 10344636, ASN 10344528 * & "INTERCHIM INTERMEDIATES" 18 January 2005 (2005-01-18), INTERCHIM , 211 BIS AV J.F. KENNEDY, BP 1140, MONTLUCON, 03103, FRANCE ----- -/--	1-4,9	
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
			C07C C07D A61K A61P
<b>INCOMPLETE SEARCH</b>			
<p>The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.</p> <p>Claims searched completely :</p> <p>Claims searched incompletely :</p> <p>Claims not searched :</p> <p>Reason for the limitation of the search:</p> <p>see sheet C</p>			
Place of search		Date of completion of the search	Examiner
The Hague		4 November 2005	Fitz, W
CATEGORY OF CITED DOCUMENTS		<p>T : theory or principle underlying the invention</p> <p>E : earlier patent document, but published on, or after the filing date</p> <p>D : document cited in the application</p> <p>L : document cited for other reasons</p> <p>&amp; : member of the same patent family, corresponding document</p>	
<p>X : particularly relevant if taken alone</p> <p>Y : particularly relevant if combined with another document of the same category</p> <p>A : technological background</p> <p>O : non-written disclosure</p> <p>P : intermediate document</p>			

7  
EPO FORM 1503 03.82 (P04C07)



European Patent  
Office

## PARTIAL EUROPEAN SEARCH REPORT

Application Number  
EP 05 01 2616

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	DATABASE CHEMCATS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002350890 * CGX 3006286, 3006283, 3006617, 3006175, 3006399, 3006653, 3006384, 3006870, 3006564, 3006319, 3006239, 3006367, 3006368, 3006847, 3006220, 3006245, 3006316, 3006317, 3006219, 3006023, 3006774, 3006541, 3006037, 3006623, 3006469, 3006533, 3006455, 3006224, 3006173, 3005918, 3006570, 3005801, 3006320, 3005885, 3006382, 3006655, 3006726, 3006372, 3006622, 3006620, 0740976, 3006379, 3006401, 3006365, 3006171, 3006733, 3006329, 3006693, 3006282, 3006350, 3006053, 3006612, 3006197, 3006656, 3006468, 3006234, 3006288, 3006508, 3006671, 3006645, 3006672, 3006257, 3006715, 3006590, 3006354, 3006687, 3006309, 3006187, 3006272, 3006036, 3006255, 3005823, 3006459, 3006461, 3006066, 3006351, 3006629, 3005816, 3006235, 3005802, 3006344, 3006248, 3005909, 3006852, 3006599, 3006603, 3006605, 0741352, 3006402, 0733817, 3006686, 3006342, 3006334, 3006216, 3005910, 3006335, 3006261, 3006246, 3006253, 3006198, 3005898, 3006311, 3005906, 3006215, 3005903, 3006028, 3006330, 3005884, 3005807, 3006043, 3005822, 3006205, 0731601, 3006229, 3006589, 3006268, 3006624, 3006571, 3006584, 3006210 * -/--	1-8	
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)



European Patent  
Office

## PARTIAL EUROPEAN SEARCH REPORT

Application Number  
EP 05 01 2616

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	& "COMGENEX PRODUCT LIST" 15 April 2005 (2005-04-15), COMGENEX INTERNATIONAL INC., PRINCETON CORPORATE PLAZA IV, 11 DEER PARK DRIVE, STE. 210, MONMOUTH, NJ, 08852, US ----- DATABASE CHEMCATS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002350889 * ASN 10348177, ASN 10348171, ASN 10348141, ASN 10348130, ASN 10348112, ASN 10347817, ASN 10347751, ASN 10345176, ASN 10344816, ASN10344636, ASN 10344528, ASN 10344487 * & "ASINEX EXPRESS PLATINUM COLLECTION" 21 February 2005 (2005-02-21), ASINEX, 5 GABRICHEVSKOGO ST. BLDG 8, MOSCOW, 123367, RUSSIA -----	1-4,9	
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	HELAL C J ET AL: "Discovery and SAR of 2-aminothiazole inhibitors of cyclin-dependent kinase 5/p25 as a potential treatment for Alzheimer's disease" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 14, no. 22, 15 November 2004 (2004-11-15), pages 5521-5525, XP004598586 ISSN: 0960-894X * title * * page 5522, table 1, compound 5 * -----	1,14,15	
A	WO 03/087842 A (ESBATECH AG; BARBERIS, ALCIDE; MIDDENDORP, OLIVER, MICHAEL; LUETHI, UR) 23 October 2003 (2003-10-23) * claim 1 * ----- -/--	1,14,15	





European Patent  
Office

## PARTIAL EUROPEAN SEARCH REPORT

Application Number  
EP 05 01 2616

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	<p>CUMMING J N ET AL: "DESIGN AND DEVELOPMENT OF BACE-1 INHIBITORS" CURRENT OPINION IN DRUG DISCOVERY AND DEVELOPMENT, CURRENT DRUGS, LONDON, GB, vol. 7, no. 4, July 2004 (2004-07), pages 536-556, XP009039538 ISSN: 1367-6733 * the whole document *</p> <p>-----</p>	1,14,15	
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)

7

EPO FORM 1503 03.02 (P/04C10)



European Patent  
Office

INCOMPLETE SEARCH  
SHEET C

Application Number  
EP 05 01 2616

Claim(s) searched completely:  
4-13

Claim(s) searched incompletely:  
1-3,14,15

Claim(s) not searched:  
-

Reason for the limitation of the search:

The present claims 1-3 and 14,15 relate to an extremely large number of possible compounds. Support and disclosure in the sense of Article 84 and 83 EPC is to be found however for only a very small proportion of the compounds claimed. For example, formula (I) includes compounds with a series of nitrogen atoms attached to each other which are commonly known to be unstable. Also, formula (I) is so broad that trivial and commonly known compounds such as diphenylurea are included in the claimed scope. The non-compliance with the substantive provisions is to such an extent, that a meaningful search of the whole claimed subject-matter of the claim could not be carried out (Rule 45 EPC and Guidelines B-VIII, 3). The extent of the search was consequently limited.

The search of claims 1-3 and 14,15 was restricted to the compounds which appear to be supported and a generalisation of their structural formulae, i.e. the compounds of claim 4 and their use.

**ANNEX TO THE EUROPEAN SEARCH REPORT  
ON EUROPEAN PATENT APPLICATION NO.**

EP 05 01 2616

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.  
The members are as contained in the European Patent Office EDP file on  
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

04-11-2005

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5814646	A	29-09-1998	NONE	
-----				
WO 03087842	A	23-10-2003	AU 2002253468 A1	27-10-2003
			CA 2482824 A1	23-10-2003
			EP 1495329 A1	12-01-2005
-----				

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

**REFERENCES CITED IN THE DESCRIPTION**

*This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.*

**Patent documents cited in the description**

- US 5814646 A [0007]
- US 5624937 A [0007]

**Non-patent literature cited in the description**

- BUDIN et al. *Biol. Chem.*, 2001, vol. 382, 1365-1372 [0030]
- HUANG ; CAFLISCH. *J. Med. Chem.*, 2004, vol. 47, 5791-5797 [0030]